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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/667,022	09/18/2003	Susan M. Freier	ISPH-0773	1420

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/667,022	FREIER ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *September 18, 2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *sequence search alignment*.

DETAILED ACTION

This Office Action is a response to Applicant's preliminary amendment filed February 27, 2004.

Claim 1 has been amended. Claims 15-20 have been canceled.

Claims 1-14 are pending in the instant application.

Claims 1-14 have been examined on the merits.

Information Disclosure Statement

Applicant's information disclosure statement filed September 18, 2003 is acknowledged. The references referred to therein have been considered on the merits.

Priority

It is noted that this application is a continuation of USSN 10/160786 filed May 31, 2002, now abandoned.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 10 is drawn to a compound 8 to 80 nucleobases in length which specifically hybridizes with at least an 8-nucleobases portion of a preferred target region on a nucleic acid molecule encoding human phosphoinositide-3-kinase, regulatory subunit 4, p150.

The specification discloses several dozen antisense oligonucleotides directed to GenBank Accession NO: Y08991.1 (represented as SEQ ID NO:4 in the instant invention) which, although sufficient to adequately describe antisense compounds directed to the human phosphoinositide-3-kinase, regulatory subunit 4, p150 (SEQ ID NO:4) do not describe compounds from any other phosphoinositide-3-kinase, regulatory subunit 4, p150. The art teaches phosphoinositide-3-kinase, regulatory subunit 4 genes with different GenBank Accession Numbers. For example, the art teaches phosphoinositide-3-kinase, regulatory subunit 4 sequences from GenBank Accession Numbers: NM_014602; XM_343466; and BC009899, for example. There is no disclosure found in the specification or known in the art that relates the structure of a compound which specifically hybridizes with at least an 8-nucleobases portion of a preferred target region on a nucleic acid molecule encoding human phosphoinositide-3-kinase, regulatory subunit 4, p150, other than SEQ ID NO:4.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

MPEP 2163 states in part, "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")."

With the exception of compounds which specifically hybridizes with at least an 8-nucleobases portion of a preferred target region on a nucleic acid molecule encoding human phosphoinositide-3-kinase, regulatory subunit 4, p150, SEQ ID NO:4, the skilled

artisan cannot envision the detailed structure of the encompassed compounds, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, only compounds which specifically hybridizes with at least an 8-nucleobases portion of a preferred target region on a nucleic acid molecule encoding human phosphoinositide-3-kinase, regulatory subunit 4, p150 directed to SEQ ID NO:4, but not the full breadth of the claim meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115).

Claim 14 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of *in vitro* (cell culture) inhibition of phosphoinositide-3-kinase, regulatory subunit 4, p150 in cells or tissues comprising administering an antisense compound targeted to the coding region of a nucleic acid molecule encoding phosphoinositide-3-kinase, regulatory subunit 4, p150, does not reasonably provide enablement for *in vivo* (whole organism) inhibition of

phosphoinositide-3-kinase, regulatory subunit 4, p150 in cells or tissues comprising administering an antisense compound targeted to a coding region of a nucleic acid molecule encoding phosphoinositide-3-kinase, regulatory subunit 4, p150. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This is a scope enablement rejection.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention, and the quantity of experimentation necessary.

Claim 14 is drawn to a method of inhibiting the expression of phosphoinositide-3-kinase, regulatory subunit 4, p150 in any cell or tissue comprising administering an antisense compound targeted to the coding region of a nucleic acid molecule encoding phosphoinositide-3-kinase, regulatory subunit 4, p150. The broadness of the method recited in claim 14 implies *in vivo* applicability of this method for enablement purposes.

The specification provides examples wherein antisense compounds targeted to a nucleic acid molecule encoding phosphoinositide-3-kinase, regulatory subunit 4, p150 inhibited the expression of phosphoinositide-3-kinase, regulatory subunit 4, p150 *in vitro* (cell culture) (see Example 15 and Table 1). The specification does not demonstrate any correlation with the inhibition of phosphoinositide-3-kinase, regulatory subunit 4,

p150 in cell culture and inhibiting the expression of phosphoinositide-3-kinase, regulatory subunit 4, p150 in any cell or tissue *in vivo* (whole organism). The specification does not present any examples wherein an antisense compound targeted to a nucleic acid molecule encoding phosphoinositide-3-kinase, regulatory subunit 4, p150 was delivered to cells *in vivo* (whole organism), nor wherein an antisense compound targeted to a nucleic acid molecule encoding phosphoinositide-3-kinase, regulatory subunit 4, p150 inhibited the expression of phosphoinositide-3-kinase, regulatory subunit 4, p150 in cells or tissues *in vivo* (whole organism).

At the time the instant invention was made, the therapeutic use of antisense was highly unpredictable due to obstacles that continue to hinder the therapeutic application of antisense therapy *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, 2000 Vol. 6:72-81), Branch, AD (TIBS, 1998 Vol. 23:45-50) and Jen et al. (Stem Cells, 2000 Vol. 18:307-319)). Such obstacles include, for example, problems with delivery, target accessibility, and the potential for unpredictable nonantisense effects. For example, Jen et al. state, "One of the major limitations for the therapeutic use of AS-ODNSs and ribozymes is the problem of delivery... Presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable" (see page 313, second column, second paragraph). Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes, "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive" (see page 315, second column). Branch addresses the unpredictability

and the problems faced in the antisense art with the following statements: "Antisense molecules and ribozymes capture the imagination with their promise of rational drug design and exquisite specificity. However, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "To minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. This is a challenging quest."; "However, their unpredictability confounds research application of nucleic acid reagents."; "Non-antisense effects are not the only impediments to rational antisense drug design. The internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,..."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "Because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. Antisense compounds are no exception. As is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "Because it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by

screening large number of candidates for their ability to act inside cells."; "Binding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. Since accessibility cannot be predicted, rational design of antisense molecules in not possible."; and, "The relationship between accessibility to oligonucleotide (ODN) binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored...It is not yet clear whether *in vitro* screening techniques...will identify ODN's that are effective *in vivo*."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo*, as broadly claimed. The specification provides examples wherein antisense compounds targeted to a nucleic acid molecule encoding phosphoinositide-3-kinase, regulatory subunit 4, p150 are delivered to cells *in vitro* and the expression of phosphoinositide-3-kinase, regulatory subunit 4, p150 is inhibited, however, cell culture examples are generally not predictive of *in vivo* inhibition due to differences in metabolites and clearance rates, local concentration of antisense, differences in target site accessibility, cellular uptake differences, and the potential for non-antisense side effects. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism) (see for example Jen et al., page 313, second column, second paragraph). Further, Agrawal et al. (Molecular Medicine Today, 2000, Vol. 6:72-81) (see page 79 and 80, section entitled *Cellular uptake facilitators for in vitro studies*) states, "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides... *In vitro*, cellular uptake of antisense oligonucleotides depends on

many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide". Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

The field of antisense, to date, does not provide guidelines by which antisense can be routinely delivered to generally any cell type *in vivo* (whole organism) at a concentration effective to result in inhibition of gene expression. The specification does not provide specific guidance by which one skilled in the art would expect to be able to deliver an antisense nucleic acid targeted to a nucleic acid molecule encoding phosphoinositide-3-kinase, regulatory subunit 4, p150 to generally any target cell or tissue *in vivo* (whole organism) at a concentration effective to inhibit phosphoinositide-3-kinase, regulatory subunit 4, p150 gene expression as encompassed by the claims.

In order to practice the invention claimed, over the full scope claimed, one skilled in the art would need to undergo undue trial and error experimentation, beyond the teachings of the instant specification. The quantity of undue experimentation would include the determination of what specific cells or tissues to target with phosphoinositide-3-kinase, regulatory subunit 4, p150 antisense compounds and how to specifically deliver antisense compounds to an organism *in vivo* (whole organism) at a concentration effective to result in the inhibition of the expression of phosphoinositide-3-kinase, regulatory subunit 4, p150. Additionally, this undue experimentation would include the determination of such factors as dosage, route of administration, disposition

of the antisense molecule in tissues, and the half-life and stability of the oligonucleotide molecule *in vivo*. Given the art recognized unpredictability of the therapeutic application of antisense *in vivo* (whole organism), this determination would not be routine and would require undue trial and error experimentation.

Therefore, due to the broad scope of the methods claimed, the state of the art of antisense therapy, the level of unpredictability of *in vivo* (whole organism) methods of using antisense, the lack of specific guidance for the *in vivo* (whole organism) application of antisense methods for *in vivo* delivery, and the lack of working examples or examples which correlate with the claimed methods, one skilled in the art would not be able to practice the methods over the full scope claimed without undue trial and error experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Monia et al. [U.S. Patent No. 6,368,856] ('856). Claim 1 is drawn to a compound 8 to 50

nucleobases in length targeted to a coding region of a nucleic acid molecule encoding human phosphoinositide-3-kinase, regulatory subunit 4, p150 (SEQ ID NO:4), wherein said compound inhibits the expression of phosphoinositide-3-kinase, regulatory subunit 4, p150. Claims 2-9 depend from claim 1 and include all the limitations of claim 1 with the further limitations wherein the compound is an antisense oligonucleotide; wherein the antisense oligonucleotide comprises at least one modified internucleoside linkage, wherein the modified internucleoside linkage is a phosphorothioate linkage, wherein the antisense oligonucleotide comprises at least one modified sugar moiety, wherein the modified sugar moiety is a 2-O-methoxyethyl sugar moiety, wherein the antisense oligonucleotide comprises at least one modified nucleobase, wherein the modified nucleobase is a 5-methylcytosine, wherein the antisense oligonucleotide is a chimeric oligonucleotide. Claim 10 is drawn to a compound 8 to 80 nucleobases in length which specifically6 hybridizes with at least an 8-nucleobases portion of a preferred target region on a nucleic acid molecule encoding human phosphoinositide-3-kinase, regulatory subunit 4, p150. Claims 11-13 depend from claim 1 and include all the limitations of claim 1 with the further limitations wherein the compound of claim 1 further comprises a pharmaceutical acceptable carrier, diluent, or colloidal dispersion system. Claim 14 is drawn to a method of inhibiting the expression of phosphoinositide-3-kinase, regulatory subunit 4, p150 in cells or tissues comprising contacting said cells or tissues with the compound of claim 1 so that expression of phosphoinositide-3-kinase, regulatory subunit 4, p150 is inhibited. It is noted that the coding region of a nucleic

acid molecule encoding phosphoinositide-3-kinase, regulatory subunit 4, p150 (SEQ ID NO:4) consists of nucleobases 577-4641 of SEQ ID NO:4.

('856) discloses a chimeric antisense phosphorothioate oligonucleotide having 2'-MOE wings targeted to phosphorylase kinase beta with the following sequence: 5'-aattcgcctg tatgcaagag-3' (see SEQ ID NO:36). ('856) also disclose that the antisense oligonucleotide represented by SEQ ID NO:36 was administered to human cells *in vitro* (see Table 1). This antisense oligonucleotide is reverse complementary to nucleobases 3672-3690 of the coding region of SEQ ID NO:4 of the instant invention (see attached sequence alignment). It is noted that the reverse complimentarity between the antisense oligonucleotide targeted to phosphorylase kinase beta disclosed by ('856) and nucleobases 3672-3690 of the coding region of SEQ ID NO:4 is not contiguous. However, the antisense oligonucleotide targeted to phosphorylase kinase beta disclosed by ('856) exhibits almost 90% local similarity to nucleobases 3672-3690 of SEQ ID NO:4 of the instant invention, as it contains only two mismatches (see attached sequence alignment). Given this high degree of similarity, the antisense oligonucleotide targeted to phosphorylase kinase beta disclosed by ('856) meets the structural limitations of the claimed invention and would be expected to "specifically hybridize" to the coding region of a nucleic acid encoding phosphoinositide-3-kinase, regulatory subunit 4, p150 (SEQ ID NO:4) since the instant specification at page 11, lines 28-31 teaches, "it is understood in the art that the sequence of an antisense compound need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable." Accordingly, the antisense oligonucleotide disclosed by ('856) would

specifically hybridize with the coding region of phosphoinositide-3-kinase, regulatory subunit 4, p150 (SEQ ID NO:4) as claimed.

The burden of establishing whether the prior art oligonucleotide has the further function of inhibiting gene expression under generally any assay conditions as instant claimed falls to Applicant. See (*In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977): "Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is based on 'inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products [footnote omitted]. See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2122 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the antisense oligonucleotide disclosed by ('856) would or would not have the additional functional limitation of "inhibiting expression" of the phosphoinositide-3-kinase, regulatory subunit 4, p150 gene (SEQ ID NO:4) under generally any assay conditions.

Therefore, absent evidence to the contrary, claims 1-14 are anticipated by ('856).

Claims 1-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Bennett et al. [U.S. Patent No. 6,410,324] ('324).

The claims are as described above in the 35 U.S.C. 102(e) rejection against claims 1-14 as being anticipated by Monia et al. [U.S. Patent No. 6,368,856] ('856).

('324) disclose a chimeric antisense phosphorothioate oligonucleotide having 2'-MOE wings targeted to tumor necrosis factor receptor 2 with the following sequence: 5'-ccacttgctcctacttgctg-3' (see SEQ ID NO:138). ('324) also disclose that the antisense oligonucleotide represented by SEQ ID NO:138 was administered to human cells *in vitro* (see Table 2). This antisense oligonucleotide is reverse complementary to nucleobases 4489-4507 of the coding region of SEQ ID NO:4 of the instant invention (see attached sequence alignment). It is noted that the reverse complimentarity between the antisense oligonucleotide targeted to tumor necrosis factor receptor 2 disclosed by ('324) and nucleobases 4489-4507 of the coding region of SEQ ID NO:4 of the instant invention is not contiguous. However, the antisense oligonucleotide targeted to tumor necrosis factor receptor 2 disclosed by ('324) exhibits almost 90% local similarity to nucleobases 4489-4507 of SEQ ID NO:4 of the instant invention, as it contains only two mismatches (see attached sequence alignment). Given this high degree of similarity, the antisense oligonucleotide targeted to tumor necrosis factor receptor 2 disclosed by ('324) meets the structural limitations of the claimed invention and would be expected to "specifically hybridize" to the coding region of a nucleic acid encoding phosphoinositide-3-kinase, regulatory subunit 4, p150 (SEQ ID NO:4) since the instant specification at page 11, lines 28-31 teaches, "it is understood in the art that

the sequence of an antisense compound need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable." Accordingly, the antisense oligonucleotide disclosed by ('324) would specifically hybridize with the coding region of phosphoinositide-3-kinase, regulatory subunit 4, p150 (SEQ ID NO:4) as claimed.

The burden of establishing whether the prior art oligonucleotide has the further function of inhibiting gene expression under generally any assay conditions as instant claimed falls to Applicant. See (*In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977): "Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is based on 'inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products [footnote omitted]. See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2122 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the antisense oligonucleotide disclosed by ('324) would or would not have the additional functional limitation of "inhibiting expression" of the phosphoinositide-3-kinase, regulatory subunit 4, p150 gene (SEQ ID NO:4) under generally any assay conditions.

Therefore, absent evidence to the contrary, claims 1-14 are anticipated by ('324).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Panaretou et al. (J. Biol. Chem., 1997 Vol. 272:2477-2485, Applicant's reference AF in the information disclosure statement filed September 18, 2003) in view of Volinia et al. (Embo J, 1995 Vol. 14:3339-3348, Applicant's reference AI in the information disclosure statement filed September 18, 2003), Agrawal et al. (Molecular Medicine Today, 2000 Vol. 6:72-81), and Baracchini et al. [U.S. Patent No. 5,801,154].

Claim 1 is drawn to a compound 8 to 50 nucleobases in length targeted to a coding region of a nucleic acid molecule encoding human phosphoinositide-3-kinase,

regulatory subunit 4, p150 (SEQ ID NO:4), wherein said compound inhibits the expression of phosphoinositide-3-kinase, regulatory subunit 4, p150. Claims 2-9 depend from claim 1 and include all the limitations of claim 1 with the further limitations wherein the compound is an antisense oligonucleotide; wherein the antisense oligonucleotide comprises at least one modified internucleoside linkage, wherein the modified internucleoside linkage is a phosphorothioate linkage, wherein the antisense oligonucleotide comprises at least one modified sugar moiety, wherein the modified sugar moiety is a 2-O-methoxyethyl sugar moiety, wherein the antisense oligonucleotide comprises at least one modified nucleobase, wherein the modified nucleobase is a 5-methylcytosine, wherein the antisense oligonucleotide is a chimeric oligonucleotide. Claim 10 is drawn to a compound 8 to 80 nucleobases in length which specifically hybridizes with at least an 8-nucleobases portion of a preferred target region on a nucleic acid molecule encoding human phosphoinositide-3-kinase, regulatory subunit 4, p150. Claims 11-13 depend from claim 1 and include all the limitations of claim 1 with the further limitations wherein the compound of claim 1 further comprises a pharmaceutical acceptable carrier, diluent, or colloidal dispersion system. Claim 14 is drawn to a method of inhibiting the expression of phosphoinositide-3-kinase, regulatory subunit 4, p150 in cells or tissues comprising contacting said cells or tissues with the compound of claim 1 so that expression of phosphoinositide-3-kinase, regulatory subunit 4, p150 is inhibited. It is noted that the coding region of a nucleic acid molecule encoding phosphoinositide-3-kinase, regulatory subunit 4, p150 (SEQ ID NO:4) consists of nucleobases 577-4641 of SEQ ID NO:4.

Panaretou et al. teach the cDNA and predicted amino acid sequence of the human phosphoinositide-3-kinase, regulatory subunit 4, p150 gene (see Figure 1). Panaretou et al. do not teach a compound targeted to the coding region of a nucleic acid molecule encoding human phosphoinositide-3-kinase, regulatory subunit 4, p150 that inhibits the expression of phosphoinositide-3-kinase, regulatory subunit 4, p150.

Volinia et al. used small molecule inhibitor, wortmannin, to elucidate the function of the phosphoinositide-3-kinase, regulatory subunit 4, p150 gene. Volinia et al. teach the involvement of phosphoinositide-3-kinase, regulatory subunit 4, p150 as part of the complex in protein trafficking from the Golgi to the lysosome (see Figure 3).

Agrawal et al. teach "antisense oligonucleotides have become efficient molecular biological tools to investigate the function of any protein in the cell" (see Abstract). Further, Agrawal et al. teach "antisense technology has become an essential laboratory tool to study and understand the function of any newly discovered genes in recent years" (see page 72, first paragraph).

Baracchini et al. teach, "oligonucleotides are designed to bind either directly to mRNA or to a selected DNA portion forming a triple stranded structure, thereby modulating the amount of mRNA made from the gene"... "the relationship between an oligonucleotide and its complementary target nucleic acid is commonly denoted as antisense"... "it is preferred to target specific genes for antisense attack"... (see column 3, lines 17-41). Baracchini et al. teach modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the

presence of nucleases. Baracchini et al. also teach antisense oligonucleotides with phosphorothioate modified backbones (see column 6, line 37)... with at least one modified sugar moiety and a modified 2'-O-methoxyethyl sugar moieties (see Table I)... with modified nucleobases, such as 5-methylcytosine (see column 7, lines 15-25). Baracchini et al. also teach an antisense oligonucleotide as a chimeric oligonucleotide (see column 8, lines 12-19). Baracchini et al. further teach antisense oligonucleotides, 20 nucleobases in length that can specifically hybridize with the coding region of a gene of interest (see column 9, lines 6-67 and column 10, lines 1-25 and Table 1).

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to make antisense compounds targeted to phosphoinositide-3-kinase, regulatory subunit 4, p150, including the target sequence of SEQ ID NO:4 using the sequence taught by Panaretou et al., the motivation of Volinia et al. and Agrawal et al., and following the method of Baracchini et al.

It would have been obvious to make antisense nucleic acids targeting to phosphoinositide-3-kinase, regulatory subunit 4, p150 (SEQ ID NO:4) since Panaretou et al. taught the sequence of phosphoinositide-3-kinase, regulatory subunit 4, p150 (SEQ ID NO:4) and Agrawal et al. teach making an antisense oligonucleotide to use as a molecular tool to investigate the function of any known protein. One of ordinary skill in the art would have been motivated to make an antisense compound targeting phosphoinositide-3-kinase, regulatory subunit 4, p150 since Volinia et al. taught the desire to inhibit the function of phosphoinositide-3-kinase, regulatory subunit 4, p150 to elucidate function in protein trafficking. One of ordinary skill in the art would have had a

reasonable expectation of success in making antisense compounds targeted to a nucleic acid molecule encoding phosphoinositide-3-kinase, regulatory subunit 4, p150 since Baracchini et al. taught the design of antisense oligonucleotides that can specifically hybridize with a gene of interest. One of ordinary skill in the art would have been motivated to make the antisense compound within the size range of 8 to 50 nucleobases for ease of synthesis and delivery and because it is conventional in the art to make antisense within this size range (as exemplified by Baracchini et al.). One of ordinary skill in the art would have been motivated to target the coding region of a nucleic acid targeted to phosphoinositide-3-kinase, regulatory subunit 4, p150 since Baracchini et al. taught antisense oligonucleotides targeted largely to the coding region of a gene of interest. One of ordinary skill in the art would have been motivated and had a reasonable expectation of success in modifying the antisense compound since the prior art has taught the desirability of such compounds are often preferred over native forms because of enhanced cellular uptake, enhanced affinity for nucleic acid target, and increased stability (see Baracchini et al.).

It would have been obvious to one of ordinary skill in the art to make a composition comprising a compound targeted to phosphoinositide-3-kinase, regulatory subunit 4, p150 and a pharmaceutically acceptable carrier, including a colloidal dispersion system because pharmaceutically acceptable carriers, including colloidal dispersion systems (e.g. liposomes) were well known in the art for use with antisense molecules as a means to deliver antisense molecules to cells *in vitro* (cell culture), as taught by Baracchini et al.

It would have been obvious to one of ordinary skill in the art to use the antisense compound targeting to phosphoinositide-3-kinase, regulatory subunit 4, p150 (SEQ ID NO:4) in a method of inhibiting the expression of phosphoinositide-3-kinase, regulatory subunit 4, p150 in cells *in vitro* (cell culture) because Baracchini et al. teach such as an obvious use for an antisense molecule targeted to a gene of interest.

Therefore, the invention as a whole would therefore have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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tcg
September 15, 2005

ANDREW WANG
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Applicants Copy

Sequence search alignment

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RESULT 99
US-09-662-250A-36/c
; Sequence 36, Application US/09662250A
; Patent No. 6368856
; GENERAL INFORMATION:
;  APPLICANT:       Brett P. Monia
;  APPLICANT:  Jacqueline Wyatt
;  TITLE OF INVENTION:       ANTISENSE MODULATION OF PHOSPHORYLASE KINASE BETA EXPRESSION
;  FILE REFERENCE:      RTS-0129
;  CURRENT APPLICATION NUMBER: US/09/662,250A
;  CURRENT FILING DATE:  2000-09-14
;  NUMBER OF SEQ ID NOS:      102
; SEQ ID NO 36
;   LENGTH: 20
;    TYPE: DNA
;    ORGANISM: Artificial Sequence
;    FEATURE:
;    OTHER INFORMATION: Antisense Oligonucleotide
US-09-662-250A-36

  Query Match           0.3%;  Score 15.8;  DB 1;  Length 20;
  Best Local Similarity   89.5%;  Pred. No. 98;
  Matches   17;  Conservative     0;  Mismatches     2;  Indels     0;  Gaps     0;

Qy       3672 TCTTACATACAGCCGAATT 3690
              |||| ||||||| ||||||
Db         19 TCTTGCATACAGGCGAATT 1


RESULT 100
US-09-844-634-138/c
; Sequence 138, Application US/09844634
; Patent No. 6410324
; GENERAL INFORMATION:
;  APPLICANT: C. Frank Bennett
;  APPLICANT:  Andrew T. Watt
;  TITLE OF INVENTION: ANTISENSE MODULATION OF TUMOR NECROSIS FACTOR RECEPTOR 2 EXPRESSI
;  FILE REFERENCE: RTS-0216
;  CURRENT APPLICATION NUMBER: US/09/844,634
;  CURRENT FILING DATE:  2001-04-27
;  NUMBER OF SEQ ID NOS: 174
; SEQ ID NO 138
;   LENGTH: 20
;    TYPE: DNA
;    ORGANISM: Artificial Sequence
;    FEATURE:
;    OTHER INFORMATION: Antisense Oligonucleotide
US-09-844-634-138

  Query Match           0.3%;  Score 15.8;  DB 1;  Length 20;
  Best Local Similarity   89.5%;  Pred. No. 98;
  Matches   17;  Conservative     0;  Mismatches     2;  Indels     0;  Gaps     0;

Qy       4489 CAGAAAGTAGGACCAAGTG 4507
              ||| |||||||| ||||||
Db         20 CAGCAAGTAGGAGCAAGTG 2
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